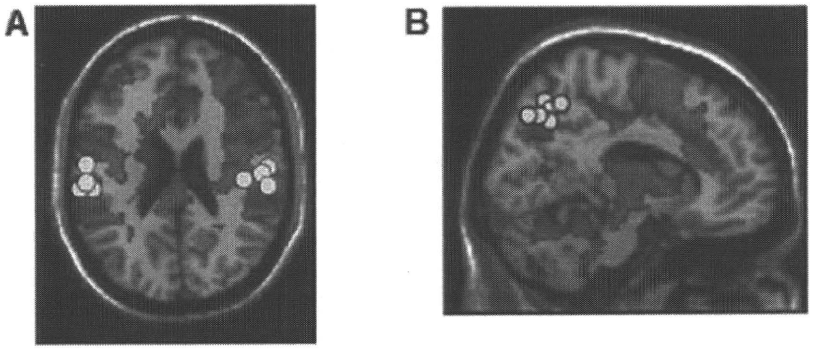

図4 MEG実験で推定されたダイポールとfMRI実験で活動した脳部位
(A) 両側前頭側頭領域の磁場反応に関係するダイポール（丸）は両側のSII/島の神経活動に関係し，(B) 頭頂領域の磁場反応に関係するダイポール（丸）は楔前部の神経活動に関係すると示唆された。MRI画像中の濃灰色部分はfMRI実験で痒み刺激に伴って活動亢進した脳部位。（文献8）より引用）。

痒みの脳内ネットワークについては良くわからない。痒みの脳内ネットワークを捉えるためには，ミリ秒単位で脳内の神経活動を計測することが必要となり，脳波や脳磁図が有用である。最近我々は，痒み刺激用の電極を作成し，痒みが誘発されるのかどうか，そして，痒み関連の脳活動（痒み誘発電位）が計測できるのかどうかを脳波を用いて調べ[21]。その結果，この痒み電極を用いて手首に電気刺激を与えると被験者は痒みを感じること，そして，痒み誘発電位も計測できることが確認された。伝導速度は約1m/secであることから，生理的な痒みと同様に，痒み電極による痒みもC線維によって伝達されることが明らかとなった。

さらに我々は，痒みのfMRIと脳磁図実験を行い，痒みに関係する脳部位の活動をミリ秒単位で計測した[22]。脳磁図実験で計測された痒み関連反応は，両側の前頭側頭領域（SIIと島）と頭頂領域（Precuneus，楔前部）に見られた。これらの領域の活動はfMRIでも確認された（**図4**）。痛みの研究では，楔前部の活動はあまり見られないことから，痒み刺激による楔前部の活動は，この部位が痛みよりも痒みに選択性をもっていることを示している。磁場反応の頂点潜時を脳部位間で比較した検討から，刺激対側のSII/島の潜時は同側SII/島の潜時よりも有意に短いことがわかった。この時間差は，脳梁を介して，刺激対側SII/島から刺激同側SII/島への情報伝達に要した時間と考えられる。この結果から，視床－刺激対側SII/島－刺激同側SII/島といった神経ネットワークの存在が示唆された。また，楔前部の潜時は刺激対側SII/島と刺激同側SII/島の中間であった。したがって，楔前部の活動は，視床－刺激対側SII/島－刺激同側SII/島という経路とは異なる，独立した神経ネットワークを形成しているのかもしれない。

おわりに

痛みや痒みの研究はこれまでは末梢受容体と脊髄レベルでの動物実験が主流であったが，今後はヒト脳内での認知機構の研究がより盛んになっていくものと思われる。痛みや痒みの認知は極めて主観的であり，ヒトを対象としなければ理解が困難な点が大きいからである。

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脳波・筋電図の臨床

不随意運動と電気生理

Involuntary movements and electrophysiological findings

魚住 武則
UOZUMI Takenori

不随意運動を正しく診断するためには綿密な観察に加えて適切な電気生理学的検査を行うことが重要である．そのためには不随意運動の発生起源（大脳皮質，基底核，フィードバック回路など），脳のリズム（振動ネットワーク）との関係，運動に関係した他の脳領域との神経ネットワーク（とくに運動前野，小脳），薬理学的にみた病態などを十分理解する必要がある．磁気刺激法の発達が不随意運動の病態解明に大きく寄与している．

KEY WORDS 不随意運動，電気生理学的検査，磁気刺激，神経ネットワーク，脳リズム

はじめに

不随意運動の正しい診断には注意深い肉眼での観察およびビデオ撮影が最も重要であるが，不随意運動の性状をさらに定量化し，病態生理学的特徴を明らかにするためにいろいろな電気生理学的検査法が行われている[1]．本稿ではその基本的検査法を概説するとともに，発生源，脳のリズム，神経ネットワーク，磁気刺激を用いた薬理学的見地などいろいろな角度から不随意運動を理解することの重要性を解説する．

不随意運動診断のための基本的電気生理学的検査

1．表面筋電図

不随意運動の客観的評価法として表面筋電図が最も有用である．表面筋電図は筋全体の活動を反映し，多数筋の活動を連続して記録することは不随意運動の分類，客観的解析に役立つ．加速度計と併用して運動と筋活動との関係をみておくことも有用である．表面筋電図で解析すべき項目は群化筋放電の出現部位，律動性，周波数，持続時間，主動筋と拮抗筋の相反性・同期性，不随意運動を誘発あるいは抑制する条件下での変化などである．とくに振戦の診断のためには，主動筋と拮抗筋での出現が相反することを確認することが重要である．一定の筋から始まり他の筋に進展していくよ

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うな不随意運動の場合，多数の筋からの同時記録を行い，最も早く筋収縮が記録される筋，筋収縮の上行・下行の様式から起源を推測することができる．後述する心因性不随意運動が疑われる場合は表面筋電図を記録しながら，姿勢との関係，出現する状況の特殊性，緊張・精神的負荷などを客観的に評価する必要がある．

2．脳波と表面筋電図の同時記録（脳波・筋電図ポリグラフ）

大脳皮質起源が推測される不随意運動の場合は表面筋電図とともに脳波も同時記録することが必要である．Creutzfeldt-Jakob病（CJD）では自発性ミオクローヌスと脳波上のperiodic synchronous discharge（PSD）と同期する場合がある．

3．誘発筋電図

末梢神経の電気刺激によって誘発される反射性筋放電は短潜時反射（H反射，筋伸張反射）と長潜時反射long-loop reflex（脊髄球脊髄反射spino-bulbo-spinal reflex，皮質経由反射transcortical reflex）に分けられる．皮質反射性ミオクローヌスでは長潜時反射は病的に増強し，C反射と呼ばれる反応が記録される．振戦に対するリセット効果をみる方法もある．振戦が生じている筋を支配する神経に対して超最大電気刺激を与えると誘発筋収縮の後の不応期に続いて振戦の周期がリセットされるが，この不応期がパーキンソン病（約200ms）と本態性振戦（100－120ms）で異なる．

4．Jerk-locked back averaging（JLA）

脳波と不随意運動に伴う筋電図を同時記録し，筋放電の立ち上がりをトリガーとして逆行性に脳波を加算平均することにより，不随意運動に先行する脳活動を記録する方法である[2]．通常の脳波・筋電図ポリグラフでは不随意運動の筋放電に伴って脳波上突発性異常が認められない場合でもこの方法で異常な脳電位が証明されることがある．皮質性ミオクローヌスでは手の不随意筋放電と対側の中心部とくに手の領域に約10～25ms先行して高振幅の脳電位を記録することができる．これは運動皮質の異常興奮を示しており，皮質性と診断できる．一方皮質下性ミオクローヌスではこのような先行脳電位は記録されない．

5．体性感覚誘発電位 somatosensory evoked potential（SEP）

皮質反射性ミオクローヌスの多くはC反射の出現に先行してSEPの皮質成分が非常に巨大（振幅10μV以上）となっている．また2連発電気刺激を与え，刺激間間隔を変えていくと巨大SEPの直後の感覚皮質興奮性の変化（SEP回復曲線）を検討できる[3]．

6．経頭蓋的磁気刺激 transcranial magnetic stimulation（TMS）

不随意運動では運動野の興奮性・抑制性が変化していることが多い．興奮性はMEP閾値が指標となる．ミオクローヌスでは低下していることが多く，抗てんかん薬の服用で高くなる．Cortical silent period（CSP）は抑制系機能の指標となる．二連発磁気刺激法を用いて運動野をいろいろな刺激間間隔でMEP閾値以下の条件刺激とMEP閾値上の試験刺激を与えると1～5msで抑制効果が認められる．詳細は後述する．

心因性不随意運動や陰性現象を見逃さない

心因性と疑われる不随意運動を呈する患者の診断は難しいことが多い[4]．以下の特徴から鑑別する．①突然出現し，突然消失することが多い．②振幅，周波数，分布が変動しやすい．③診察時や観察中は増悪し，誰もいなくなると緩解する．④placeboやsuggestionで増悪あるいは緩解する．⑤注意をそらすと著減する．その際はかなり集中しないとできないような複雑な課題を与えるのが効果的である．⑥心理的背景（抑うつ，疾病利得など）が存在する．また不随意運動は筋収縮だけでなく，筋収縮が維持できない陰性現象のことも

あり，ミオクローヌスやジストニアなどでしばしば観察される．診断に迷ったらビデオ撮影や表面筋電図での確認を繰り返す．

不随意運動を発生源から考える

1．大脳皮質を主な起源とするもの

すべての運動の最終共通路は一次運動野から発するが，その異常興奮によって勝手に筋が収縮する代表的なものがミオクローヌスである．ミオクローヌスは突然生じる瞬間的でjerkyな不随意運動であり，短い筋収縮によって生じる陽性ミオクローヌスと持続的筋収縮が突然消失する陰性ミオクローヌスに分けられる．発生起源からは主に皮質性，皮質下性，脊髄性の3つに分類される．さらに網様体性，propriospinal myoclonusも追加される．そのなかで最も多いものが大脳皮質を起源とする皮質性ミオクローヌスである．皮質性はさらに自発性（刺激と無関係に生じる），皮質反射性（刺激過敏性があり，体性感覚，聴覚，視覚刺激などで誘発される），持続性部分てんかん発作epilepsia partalis continua（EPC）に分けられる．表1にミオクローヌスの主な電気生理学的検査法を示すが多くは皮質性ミオクローヌスの診断に重要なものである．propriospinal myoclonusなどの診断には多数筋からの表面筋電図が必要である（図1）[5]．またミオクローヌスでも律動性に生じるものがある．皮質下性（CJDでPSDに関係したもの，アルツハイマー病の一部），脊髄性，皮質性（大脳皮質基底核変性症でのクローヌス様のもの，familial cortical myoclonic tremor with epilepsyでの振戦様のもの）などである．Mirror movementsも皮質性起源に含まれ，脳梁を介した抑制機能の異常に錐体交叉の異常が加わり複雑なパターンを示す．

表1　ミオクローヌス診断に必要な電気生理学的検査法

- 表面筋電図（拮抗筋が同期、どの筋から始まるか）
- Giant SEP（10μV以上）
- Jerk-locked back averaging法（JLA法）による先行棘波
- Long-loop reflexの亢進（C反射）
- 磁気刺激（運動閾値の低下）
- SEP回復曲線

2．基底核運動ループを主な起源とするもの

基底核運動ループは一次運動野，大脳皮質運動関連領野と主に被殻を結ぶもので運動の遂行に関係し[6]，下記の3つの基底核神経回路で調節されている．ハイパー直接路は大脳皮質から興奮性入力を受けた視床下核ニューロン出力核のGABA作動性ニューロンに単シナプス性に最も短時間に投射する経路である．これによりまず視床－大脳皮質投射ニューロンが広く抑制される．直接路はGABAとサブスタンスPを持つ線条体ニューロンが出力核に単シナプス性に投射する経路で基底核出力を減少させ（脱抑制）随意運動に必要な標的ニューロンが活動する．最後に働くのが間接路であり，GABAとエンケファリンを持つ線条体ニューロンが多シナプス性に淡蒼球外節のGABA作動性ニューロンと視床下核のグルタミン作動性ニューロンを介して主力核に投射し，標的ニューロンの活動は再び抑制される．このように大脳皮質の状態やそこで取り得る運動を報酬予測に基づいて評価し，それによって運動系列や行動様式を選択している．さらに図2に示すように基底核には意図した運動以外の競合する運動を抑制する働き（周辺抑制：surround inhibition）があり，時間的空間的に運動をコントロールしている[7]．基底核運動ループの異常あるいは周辺抑制の異常によって下記に示すさまざまな不随意運動が生じる．

1）ジストニア

ジストニアとは筋の持続のやや長い収縮で生じるものでジストニア姿勢とジストニア運動からなる．前者は異常収縮の結果としての異常姿勢・異常姿位で，後者は異常収縮によるゆっくりした運動であり，これらはその症例にとって定型的であり，動作特異性や常同性，感覚トリックという特徴を有する．表面筋電図では特定の動作で主動筋と拮抗筋が持続性に共収縮するが動作によってはバースト状に相反性に収縮することもある．ジストニアの発生機序は運動サブルーチン（特定の動

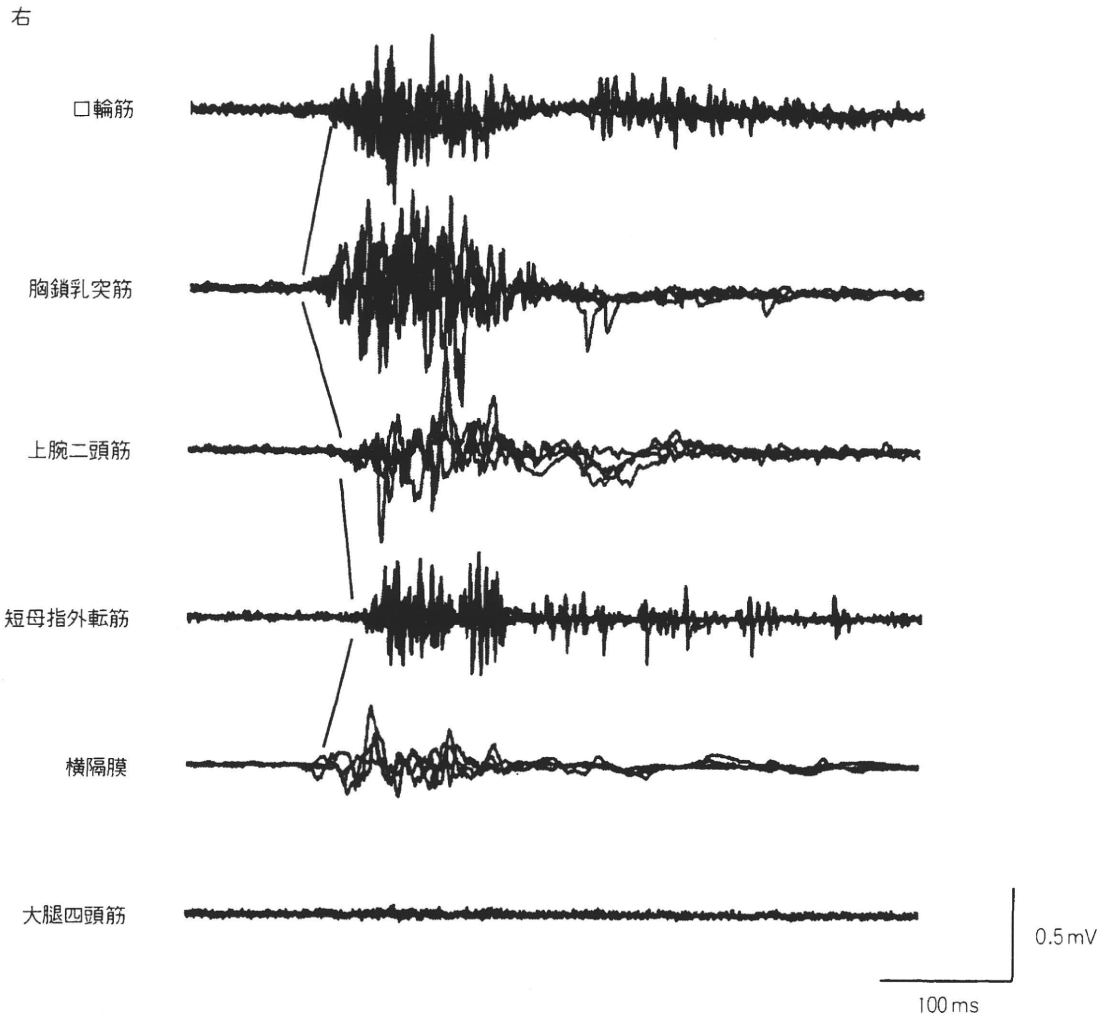

図1　propriospinal myoclonus における表面筋電図
胸鎖乳突筋から始まり，上下に進展することがわかる．

作を繰り返す場合，その動作に必要な固有知覚入力を基に大脳皮質と基底核の間に形成された一定の運動出力）の異常と考えられている．ドーパミンの相対的・絶対的過剰からみると直接路（D1）の過興奮および間接路（D2）の異常による淡蒼球外節の過興奮，視床下核の抑制の結果，淡蒼球内節からの抑制性出力が抑制（脱抑制）されジストニアが生じると考えられている．その結果として運動出力の亢進による個々の筋活動の増加と周辺抑制の低下によって目的に焦点が絞れた運動ができず，競合する筋まで収縮が生じてしまうことになる[8]．周辺抑制機能の評価にはH波やTMSが用いられている．主動筋は運動開始前約100 msから発火まで興奮性が増大し，拮抗筋には相反性抑制がかかっている．図3に示すように正常者では運動準備段階での主動筋（短母指外転筋）のMEP増大と拮抗筋（第一背側骨間筋）のMEP抑制が認められるがジストニア患者では拮抗筋の抑制が障害されている．またMEP変動も正常者では刺激毎に潜時・振幅ともかなり変動するがジストニア患者ではほとんど変動しない（図4）．

2）アテトーゼ

アテトーゼは主として四肢遠位部に絶えず繰り返しみられる緩徐な筋緊張の変動により回転性のよじるような動きである．主動筋と拮抗筋は同期して収縮し，共同運動が困難で各筋がゆっくり勝手に動くので一定の姿勢を保持できない．原因疾患としては脳性麻痺が最も多い．表面筋電図では1～3秒持続する自発的な非律動性群化放電が主動筋と拮抗筋に同期して記録される．

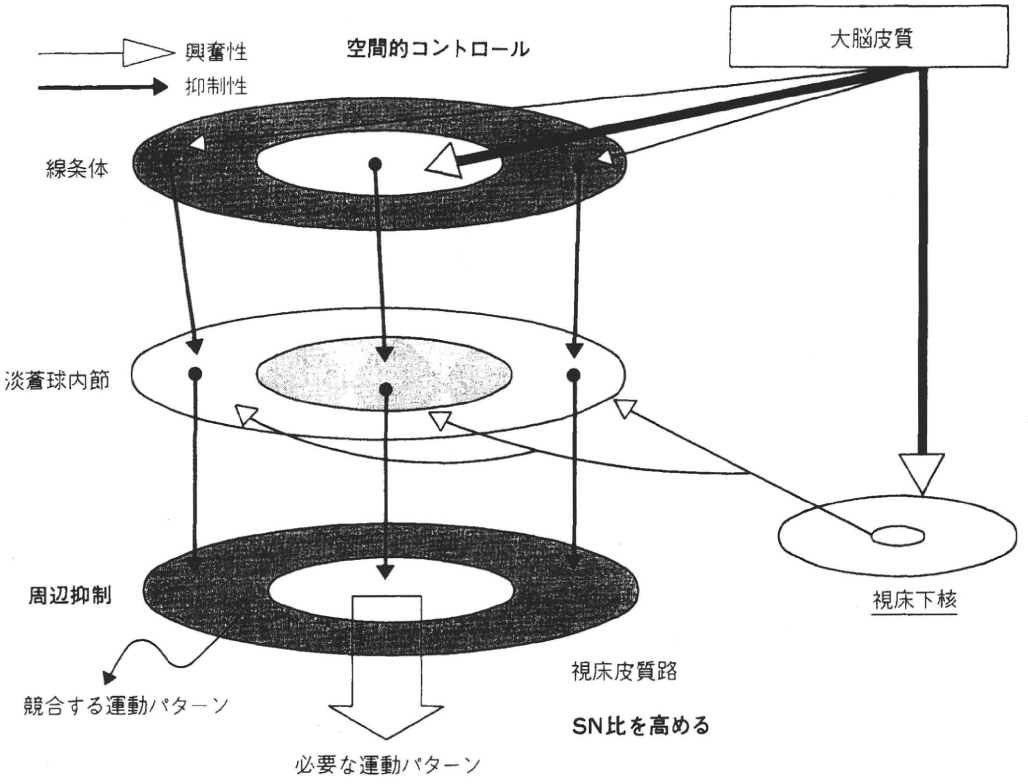

図2　周辺抑制の機能
(Mink JW:2004[7] を改変)

3）舞踏症（舞踏運動）

舞踏症は比較的速く，出現間隔も大きさもまったく不規則な，顔面，四肢，体幹に及ぶ全身性の不随意運動である．精神的緊張や随意運動で増強することが多い．眉をしかめたり，首をすくめたり，手指を進展・屈曲させたりといった落ち着きがない状態と受け止められやすい．表面筋電図では50～300ms 位の持続を持つバースト状の筋放電が間隔も大きさも不規則にいろいろな筋に出現する．舞踏症の発生機序としては間接路の異常と考えられており，線条体から淡蒼球外節への抑制がとれることにより，視床下核への抑制が増強し，淡蒼球内節への興奮性作用が低下するために，淡蒼球内節からの抑制性出力が低下し，随意運動を妨げる運動や不要な運動を抑制できなくなるために運動過多となる．

4）バリスム

バリスムは上肢あるいは下肢を投げ出すような激しい動きで片側性のことが多い（片側バリスム）．回旋性要素を伴い，同じパターンの動きを繰り返すが，律動性はない．バリスムは主に視床下核を中心とした間接路が選択的に障害されることにより，視床への抑制がとれて出現する．血管障害や高血糖が原因として多い．被殻淡蒼球病変の関与も推測されている．

3．運動のフィードバック回路を主な起源とするもの

振戦は不随意運動で最も頻度が多いものであるがその発生機序はまだ十分解明されていない．運動をうまく調節するためには主に3つのフィードバック回路が関与していると考えられており，その障害が振戦の発生に関係していることが推測されている[9]．末梢要因として単シナプス性脊髄反射（筋伸長反射）があげられる．中枢要因としては小脳ループと基底核運動ループがあげられる．前者は，大脳皮質－橋核－対側の小脳半球－歯状核－上小脳脚交叉－同側の視床－大脳皮質を中心とした経路である．これらのフィードバックの時間差によって生じた異常振動と中枢での神経細胞

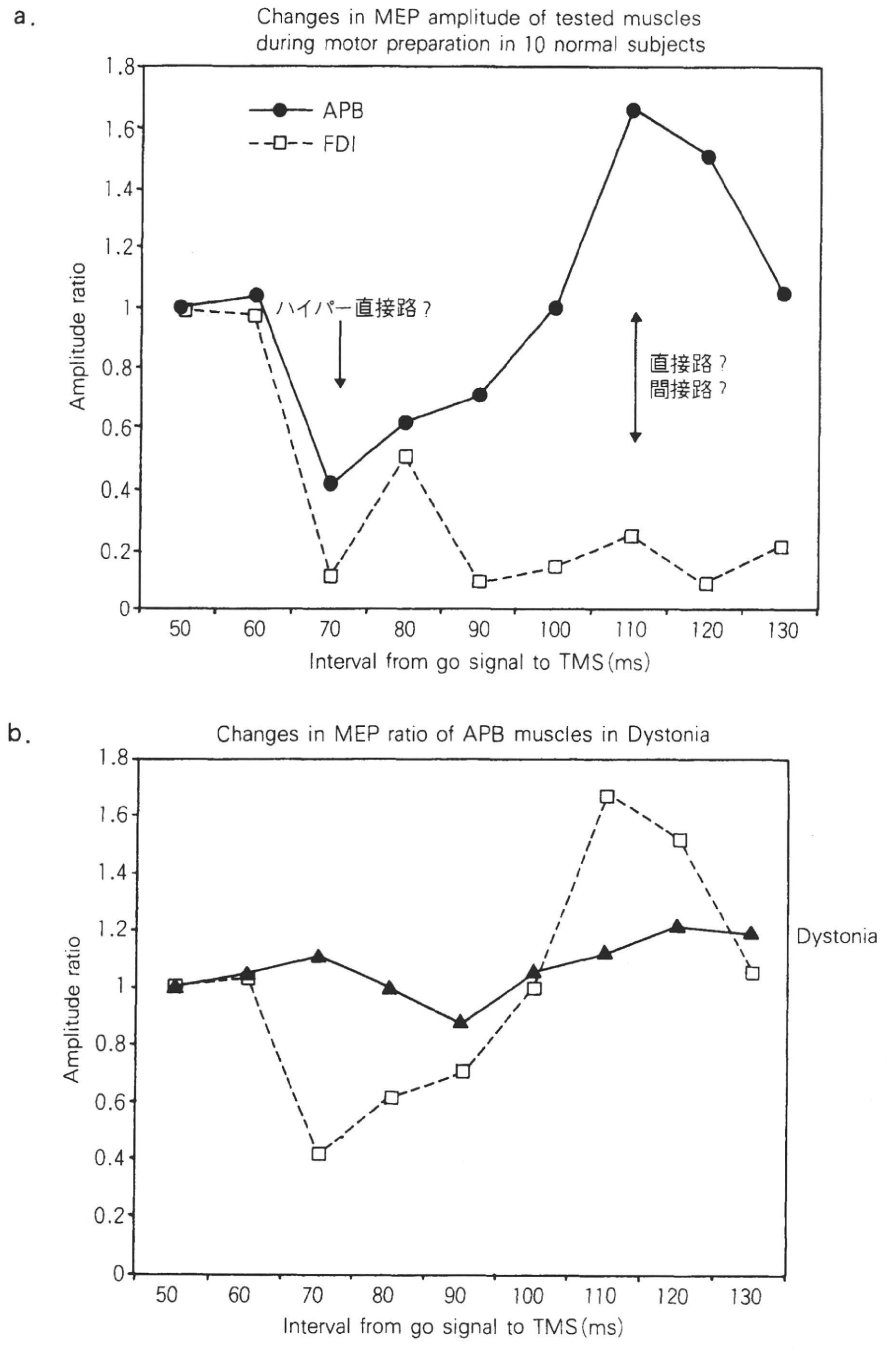

図 3

a：正常者での運動準備段階での主動筋（短母指外転筋）のMEP増大と拮抗筋（第一背側骨間筋）のMEP抑制.
b：ジストニア患者での拮抗筋抑制の障害.

固有の周波数を有する振動（下オリーブ核，視床など）が主な振戦源となる．原則としてフィードバック回路が長ければ振戦の周波数は低くなるし，神経細胞固有の振動に起因した振戦は感覚入力の影響を受けにくい．Parkinson病における安静時振戦は3～6Hzの安静時振戦が片側の上肢から始まることが多い．この振戦の発生には基底核運動ループと小脳ループが相互に関与していることが推測されているがとくに淡蒼球内節と視床下核が重要視されている．

本態性振戦は最も頻度が多い不随意運動であり，両手および両前腕の姿勢時または運動時振戦が主体で，頭部，舌の振戦がみられることがある．周波数は4～12HzでParkinson病の振戦より高い．本

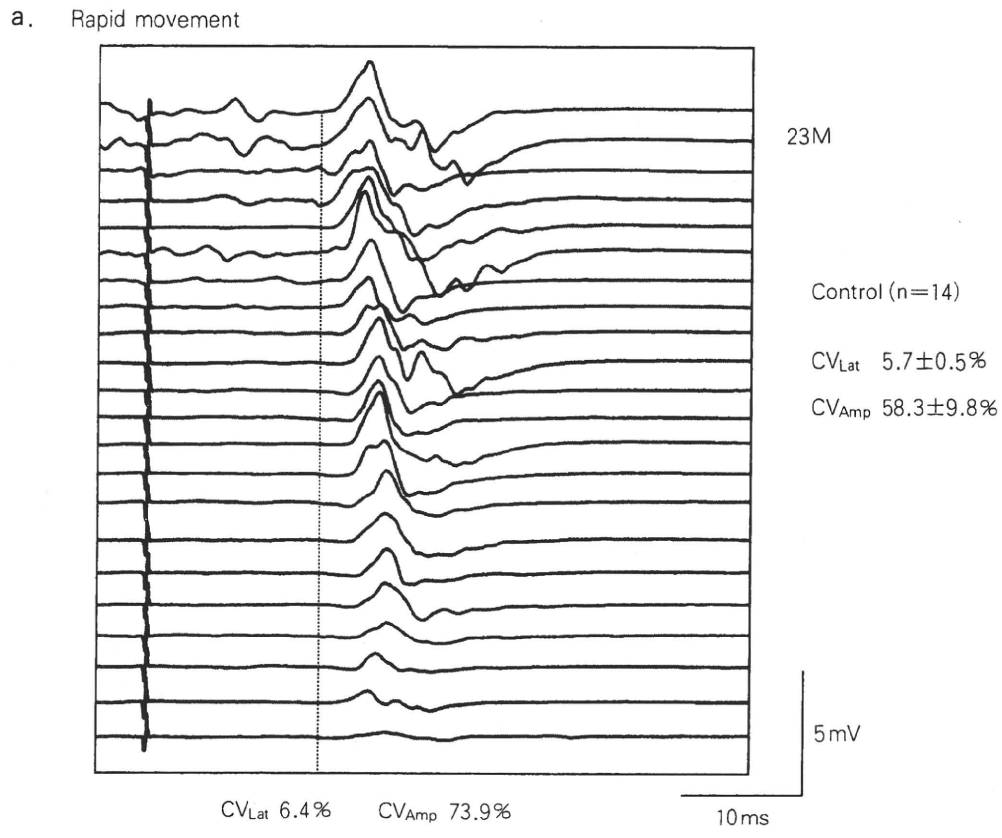

図 4

a：正常者での MEP 変動.

b：ジストニア患者における MEP 変動の著減.

態性振戦の発生起源は未だ確立していないが，末梢起源説よりも中枢起源説（とくに下オリーブ核－小脳系あるいは大脳感覚運動野）が有力である．

動作時振戦・企図振戦は運動の開始直後から始まり，動作が終わると消失する振戦が動作時振戦である．指鼻試験では鼻に到達すると揺れは止まる．

企図振戦は動作に伴って生じる3～6Hzの振戦であり，目的に向かうに従って増強し，かつその姿勢を保つ間も振戦が持続する．いずれも小脳遠心路（上小脳脚を経由する）の障害と考えられている．Holmes振戦（中脳振戦）は安静時および動作時に生じる3Hz程度のゆっくりとした振戦である．Guillain-Mollaret三角（歯状核－対側の赤核－下オリーブ核）の障害とくに赤核周辺の障害から数週から数ヵ月経過して新たな神経結合が生じた結果振戦が生じると考えられている．口蓋振戦は2～3Hzの軟口蓋の振戦であり，喉頭・横隔膜にも生じることがあり，Guillain-Mollaret三角の障害で生じる．

不随意運動を脳のリズムから考える

脳は莫大な数のニューロンが結合した結合振動子系であるという．随意運動に関連してもいくつかの振動ネットワークが存在する．たとえば運動の直前と遂行中に対側の感覚運動野に40～50Hz gamma帯域のevent-related synchronization（ERS）が生じる．また運動終了1～2秒後には15～25Hz beta帯域のERSが認められる．それらの異常が一部の不随意運動の発症にかかわっていると考えられる．また，てんかん患者でも発作開始時にvery fast oscillations（80～500Hz）が認められることがある．4～7Hz oscillationは広い神経ネットワークにかかわり，$GABA_A$抑制に関係すること，15～25Hzはidlingあるいは運動準備状態に関係すること，40～50Hzは局所の神経活動に関与すると考えられている．とくに皮質性ミオクローヌスではあるリズムで皮質興奮性が変動しており[10]，そのリズムを確認するために有用な検査法としてpaired-pulse TMSとjerk-locked MEPがある．

1．15～25Hz oscillation

皮質反射性ミオクローヌスでは二重ときには三重にC反射が誘発されることがある．これらの多重C反射間の潜時差はほとんど40～50msである．JLA法を用いて，C反射に先行する脳波の変化を記録するとC反射と同じリズムで律動性脳波活動が記録される．さらに自発性ミオクローヌスあるいはC反射をトリガーにして刺激間隔を変えながら手の運動野をMEP閾値下の強度で磁気刺激する（jerk-locked MEP）とあるタイミングで磁気刺激した場合にMEPが容易に記録され，このタイミングでは運動野の興奮性が亢進していることが推測され，このときのミオクローヌスあるいはC反射とMEPの潜時差は40～50msである．下肢のみに皮質性ミオクローヌスを呈した1例においてEEG-EMGポリグラフで下肢筋の律動性ミオクローヌスに対応して中心部頭皮上からそれと同じリズムの20～25Hz律動性脳波活動が記録された（図5）．上肢筋と同様にJLA法においてミオクローヌスの前後での律動性脳波活動が下肢の一次運動野付近の頭皮上から記録された．paired-pulse TMSでは刺激間隔45～40msでMEPが容易に刺激された．このように皮質反射性ミオクローヌスを呈した症例の多くで15～25Hzのoscillationが認められ，beta ERSとの関連性が推測される[11]．

2．40～50Hz oscillation

動作性ミオクローヌスを呈した患者では40～50Hz oscillationを示すことが多い．低酸素脳症後に動作性ミオクローヌスを生じた1例を検討するとすばやくボタンを押す動作をさせた場合は約50Hzのリズムを有する筋放電パターンを示し，EEG-EMGポリグラフにおいても筋活動に先行して同じリズムの律動性脳波が記録された．JLA法を用いた検査ではミオクローヌス筋放電に約30ms先行して対側の中心部に脳波上棘波が認められた．paired-pulse TMSでも同様のリズムの

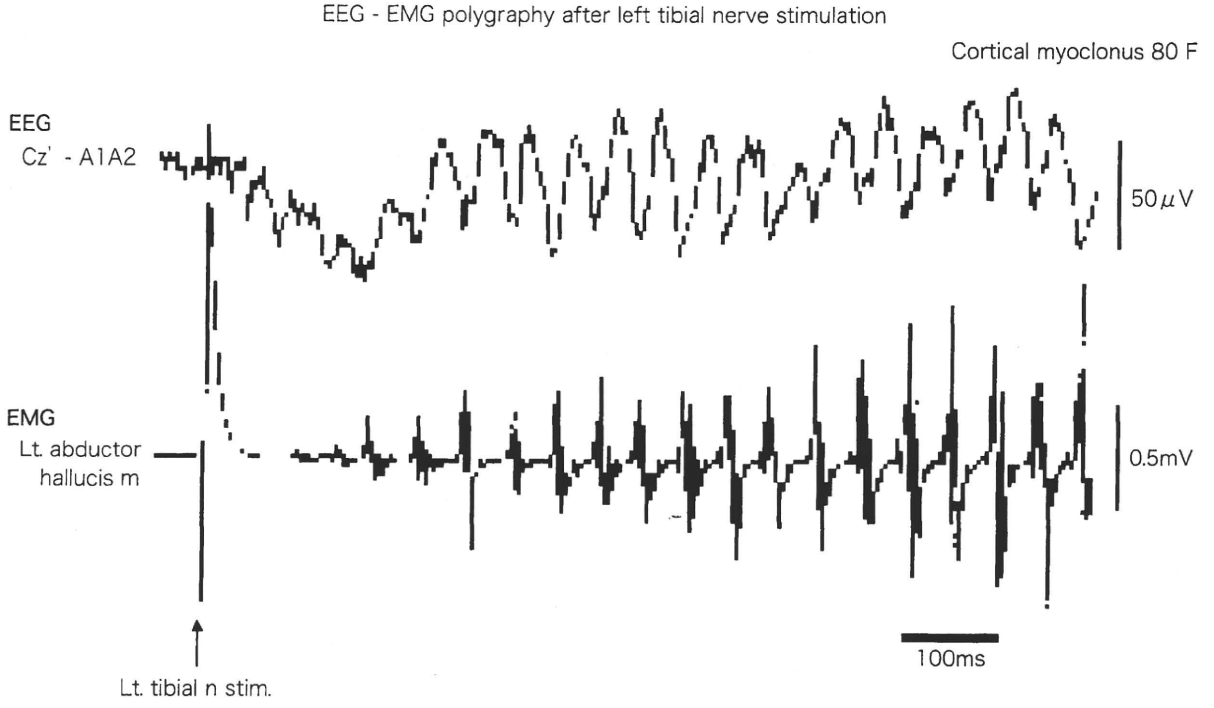

図5　律動性皮質性ミオクローヌス患者で認められた20Hz oscillation

興奮性の変化が証明された[12]．このような動作性ミオクローヌスでは動作時に40～50Hzのoscillationが認められ，随意運動時に観察されるgamma ERSとの関連が推測される．

3．very fast oscillation（80～500Hz）

運動系においても他の大脳皮質と同様にvery fast oscillationが存在することが推測されるがそれを示す十分な証拠は乏しい．C反射は通常はsimpleな波形を示すが時に多相性となる場合がある．各ピークの間隔は2.5～4ms（250～400Hz）であり，very fast oscillationが亢進している可能性が考えられた[13]．また，TMS後に錐体路ニューロンに生じるmultiple I wavesも周期性放電であり，その発射頻度は約500～700Hzである．これが体性感覚野や視覚野で認められるhigh frequency oscillations（HFOs）と同じ機序あるいは意義を持つのか不明である．しかし，ある種のてんかんでvery fast oscillationの亢進が観察され，ミオクローヌス患者で感覚野のHFOsが高振幅であることが報告されており[14]，皮質興奮性の異常を生じる点では共通点がある．

4．大脳皮質基底核変性症（CBD）におけるoscillation

CBDにおけるミオクローヌスは他の疾患で認められるミオクローヌスと比べて以下に示すような異なった特徴を有する．①運動拙劣を示す上肢に目立つ，②安静時よりも動作時に顕著となり，特に指を押すなどの負荷を与えて筋緊張を高めることで誘発されやすく，その場合は一見律動性で（6～7Hz）クローヌス様に見える，③giant SEPは認められず，むしろ皮質反応は低振幅のことが多い，④JLA法でもpremyoclonic spikeが認められない，⑤C反射は記録されるがその潜時差から計算されるcortical delay timeは短く，感覚野経由した反射とは考えにくい，⑥40～50Hzのoscillationが認められることが多い．EEG-EMGポリグラフにおいて約40Hzの律動性活動が記録された症例での自発性ミオクローヌスをトリガーとしたjerk-locked MEPではC反射と23msの間隔でMEPが誘発される刺激タイミングにおいて皮質興奮性が亢進していることが示された．

不随意運動を神経ネットワークから考える

M1の出力に影響を与える大脳皮質領域は多数存在するが，とくに運動前野（PMd，PMv）補足運動野，頭頂葉後部（PPC），感覚野が重要である．また小脳からの影響も重要である．これらのネットワーク機能をみる方法としてその領域にTMSあるいはrTMSを条件刺激として与え，MEPへの影響をみることが行われている[15]．

1．運動前野刺激

同側のPMdに対して閾値下の単発TMSあるいは1 Hz rTMSを与えるとMEPは振幅低下し，5 Hz rTMSでは振幅増大する．これらの方法を用いてジストニアでのPMd-M1抑制性結合低下が証明されている[16]．さらには二重条件刺激の影響や対側のPMdからの影響も検討されている．

2．小脳刺激

小脳にTMSを与えることにより大脳皮質運動野へのTMSあるいは電気刺激により導出されるMEPが抑制され，小脳失調患者では異常となることが報告されている[17]．小脳条件刺激のためにはダブルコーンコイルの中心を後頭孔隆起上と外耳孔を結ぶ線上を後頭孔隆起より3 cm外側の部位に置き，コントロール波形に比べて，刺激間隔5 msで抑制が始まり，3～4 ms抑制が持続する．この効果は小脳刺激によって小脳皮質のプルキンエ細胞が刺激され，歯状核にインパルスが伝わり，小脳－視床－大脳皮質回路が賦活化され，皮質運動野を抑制することが推測されている

上腕二頭筋を随意収縮した状態でダブルコーンコイルを用いて小脳外側部にTMSを加えると同側の上腕二頭筋から潜時約26～28msで促通効果が生じ，それに続いて約50ms持続する抑制効果が認められる．右視床出血後6ヵ月経過した頃から左上肢の協調運動障害に加えて約3 Hzの動作時振戦を認めた患者で小脳核視床路の障害が推測されたが，この方法での左上腕二頭筋での反応が消失していた[18]．

薬理学的に不随意運動を考えてみる

TMSを用いた運動野の興奮性をみる検査法は表2に示すように多数開発されている．しかもそ

表 2

a：運動野興奮性をみるためのMEP測定法

Single TMS
Motor threshold（MT）
MEP amplitude（MEP）
Cortical silent period（CSP）
Paired TMS
Short-interval intracortical inhibition（SICI）：1－5 ms
Intracortical facilitation（ICF）：7－20ms
Short-interval intracortical facilitation（SICF）：約1.5ms毎
Long-interval intracortical inhibition（LICI）：50－200ms
末梢神経刺激
Short latency afferent inhibition（SAI）：2－8 ms

b：TMSと薬理学的意義

MT：Na^+channel阻害剤で低下
MEP：$GABA_AR$ agonistsで低下，SSRIで上昇など
CSP：$GABA_AR$を反映．強刺激で$GABA^BR$も
SICI：$GABA_AR$を反映
ICF：GABA? glutamate?
SICF：興奮性介在ニューロン（I wave産生）
LICI：$GABA_BR$を反映
SAI：cholinergic function?

の薬理学的意義もかなり解明されており，これらの方法を用いてそれらの薬理学的異常がヒトでも検討できるようになってきた[19]．とくに不随意運動において研究が進んでおり，ミオクローヌスではshort-interval intracortical inhibition（SICI）の低下とintracortical facilitation（ICF）の亢進，本態性振戦ではICFの亢進，ジストニアではCSPの短縮，SICIの低下およびshort latency afferent inhibition（SAI）の亢進，舞踏様運動ではCSPの短縮，SICIの減弱，long-interval intracortical inhibition（LICI）の亢進およびICFの亢進，チックではSICIの短縮などが報告されている．

おわりに

不随意運動を理解するには，その発生起源や病態を考えて検査法を選択する必要がある．磁気刺激法などの検査法の発展により，病態生理の解明が進むものと期待される．

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Global cerebral hypoperfusion in preclinical stage of idiopathic normal pressure hydrocephalus ☆

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ABSTRACT

In patients with idiopathic normal pressure hydrocephalus (iNPH), ventriculomegaly and narrowed subarachnoid spaces at the high convexity appear in magnetic resonance (MR) images before the occurrence of objective symptoms. In addition, quantitative regional cerebral blood flow (rCBF) has been reported to be reduced in iNPH patients with objective symptoms. To determine whether reduced rCBF is responsible for the appearance of symptoms, we compared rCBF in patients with suspected iNPH with no objective triad symptoms (NOS), iNPH patients with apparent objective triad symptoms (AOS) and normal control subjects (NC). Regional CBF was quantified in 35 Regions-of-interest (ROIs) by 123I-IMP single photon emission computed tomography (SPECT) using the autoradiography (ARG) method. Multiple comparisons showed that, in all brain regions examined except for in the frontal white matter, rCBF in the NOS group was significantly lower than that in the NC group, but in all brain regions, not significantly different from that of the AOS group. These results suggest that factors other than rCBF in the resting state are responsible for the occurrence of objective symptoms of iNPH.

1. Introduction

Normal pressure hydrocephalus (NPH) is a treatable syndrome accompanied by a progressive triad of gait disturbance, cognitive impairment and urinary incontinence resulting from ventricular enlargement, and is associated with normal cerebrospinal fluid (CSF) pressure [1]. Idiopathic NPH most commonly occurs in the sixth to eighth decades of life without an identifiable causative antecedent disease. Both ventriculomegaly and a narrowed subarachnoid at the high convexity are observed in brain magnetic resonance (MR) images in about one percent of normal elderly subjects as well as in patients with iNPH [2]. Quantitative regional cerebral blood flow (rCBF) seemed to be reduced in iNPH patients [3], which raises the question whether quantitative rCBF is also reduced in patients with pre-clinical stage iNPH.

Kitagaki et al. observed narrowed subarachnoid spaces at the high convexity and enlarged sylvian fissures, as well as ventriculomegaly, in patients with iNPH [4]. In fact, the narrowed subarachnoid spaces at the high convexity on computed tomography images or MR images was used as an inclusion criterion for iNPH patients in some previous studies [5–7]. A recent epidemiological study in Japan reported a combination of ventriculomegaly and narrowed subarachnoid spaces at the high convexity on MR images in 12 (1.5%) of 790 community-dwelling elderly subjects [2]. Eight (1.0%) of the subjects had none of the triad symptoms, leading the authors to diagnose the subjects as having "asymptomatic ventriculomegaly with features of idiopathic normal pressure hydrocephalus on MRI (AVIM)". Two (25%) of the eight subjects with AVIM developed cognitive impairment and/or gait disturbance during 4–8 years follow-up. Thus, AVIM may be a preclinical stage of iNPH and patients with AVIM might provide clues to the neuropathological mechanism of the triad symptoms of iNPH.

There is some evidence that the cerebral vasculature has a role in the occurrence of symptoms of NPH, especially in iNPH [8,9]. Several studies seemed to show an association between rCBF reduction and the appearance of clinical symptoms, although there were some inconsistencies in the data [3,7,10–19]. The inconsistencies can be attributed to a number of methodological problems: (1) relative rCBF

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was analyzed in most of the studies [7,17,18], although quantitative rCBF could decrease over broad regions of the brain in patients with iNPH [3]. (2) In some of the studies, rCBF was analyzed by a voxel-wise comparison technique, such as statistical parametric mapping (SPM) [7,17] or three-dimensional stereotactic surface projections (3D-SSP) [18], although the brains of iNPH patients were too severely distorted to be mapped by the automated voxel-wise comparison technique [18]. (3) In studies using region of interest (ROI) analyses, the number of ROIs was limited [3]. (4) Some of the studies included not only patients with iNPH but also patients with secondary NPH [12,14,20]. (5) Some studies measured rCBF in iNPH patients that were experiencing small improvements of symptoms after shunt-operations [17].

Because hypoperfusion has been observed in several brain regions in iNPH patients with triad symptoms [11–13,21], we hypothesized that hypoperfusion would not be detected in the brains of suspected iNPH patients with no objective symptoms. To test this hypothesis, we recruited patients with iNPH-associated MR image features with and without objective triad symptoms. For controls, we used existing data for normal elderly subjects. We then compared the quantitative rCBF of the 16 brain regions among the three groups.

2. Methods

This study was approved by the Ethical Committee, Osaka University Graduate School of Medicine. Written informed consent was obtained from both subjects and their caregivers.

2.1. Subjects

For our study, we recruited patients with suspected iNPH from patients who visited the neuropsychological clinic in the Department of Neuropsychiatry of Osaka University Medical Hospital from 1 May 2007 to 31 December 2008. Inclusion criteria for the study were (1) age >60 years, (2) both ventricular dilatation (Evans index >0.3) and narrowed subarachnoid spaces at the high convexity without severe cortical atrophy, shown on MR images, (3) absence of diseases or conditions that could cause the clinical symptoms or radiological findings, (4) no history or evidence of conditions that might cause secondary NPH. During the above period, we recruited 14 patients, with a mean age of 73.1 ± 4.6 years (range, 64–80 years) and a mean educational attainment of 13.4 ± 2.9 years (range, 9–16 years).

The iNPH grading scale (iNPHGS) [22] is a clinician-rated scale to separately rate the severity of each of the triad symptoms of iNPH. The score of each domain ranges from 0 to 4. Zero indicates normal and one indicates having subjective symptoms without objective symptoms. Two to four indicate having apparent objective symptoms, in which higher scores indicate worse symptoms. In the gait domain, the condition of score 1 was complaint of dizziness of drift and dysbasia but no objective gait disturbance and that of score 2 was an unstable, but independent gait. In the cognitive domain, the condition of score 1 was a complaint of amnesia or inattention but no objective memory or attentional impairment and that of score 2 was amnesia or inattention, but no disorientation of time or place. In the urinary domain, the condition of score 1 was pollakiuria or urinary urgency and that of score 2 was occasional urinary incontinence (1–3 or more times per week but less than once per day).

We evaluated the triad symptoms of the 14 iNPH patients with iNPHGS and divided the patients into two groups according to the iNPHGS scores. One group consisted of seven patients whose iNPHGS scores for all triad domains were 0 or 1. We designated this group as suspected iNPH patients with no objective triad symptoms (NOS) (Fig. 1, Table 1). All seven patients had a score of 1 in at least one of the triad domains. They thus differ from AVIM individuals who were defined as showing no neurological symptoms or signs (although the scale by which symptoms were measured was not given) [2]. The NOS group consisted of six males and one female. Their mean age was 72.7 ± 5.7 years (range, 64–80 years), mean morbidity duration was 3.2 ± 2.4 years (range, 0.5–6 years) and mean educational attainment was 13.9 ± 2.5 years (range, 9–16 years).

The other group consisted of seven patients who had an iNPHGS score of 2 or more in at least in one of the triad domains and were called iNPH patients with apparent objective triad symptoms (AOS) (Table 1). The AOS group consisted of four males and three females. Their mean age was 73.6 ± 3.6 years (range, 68–79 years), mean morbidity duration was 2.9 ± 1.3 years (range, 1–5 years) and mean educational attainment of 12.9 ± 3.4 years (range, 9–16 years). The mean value of CSF opening pressure of the AOS group was 163.6 ± 25.4 mmH2O (range, 140–205), which met the criteria of normal pressure (70–245 mmH2O) [23]. The CSF of all of the AOS patients was clear and had no abnormalities. The symptoms of all of the AOS patients transiently improved after discharge of 30 ml of CSF [24]. Four of the patients subsequently underwent a lumbo-peritoneal shunt (LP-shunt) operation, and all of them improved as a result of it.

For single photon emission computed tomography (SPECT) data for normal subjects, we used existing SPECT data for 34 subjects. These 34 subjects were selected from the 147 normal controls for a previous study [25], according to the following criteria. They were aged 60 years or older and lived in their own homes or in homes for the independent elderly. The inclusion criteria of the normal elderly

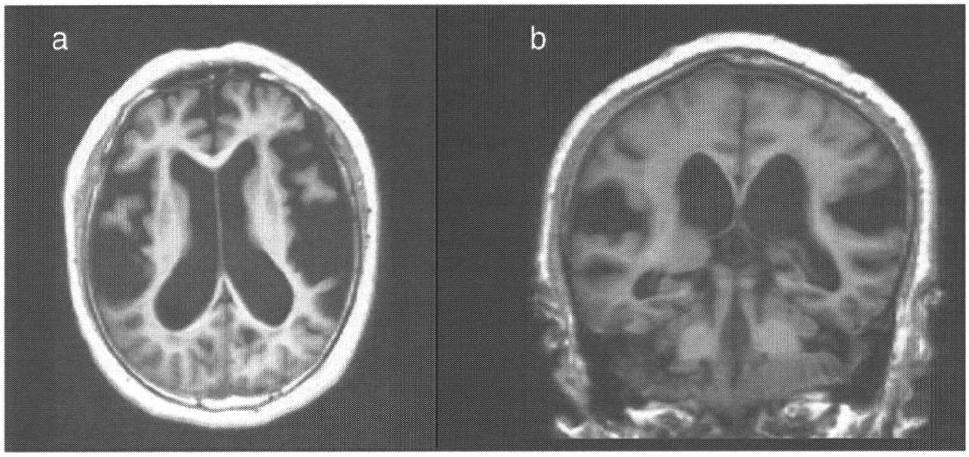

Fig. 1. Brain MR images of a NOS patient. (a) and (b) are MR images of an 80-year-old male patient with NOS (NOS 4). His MMSE score was 28/30. NOS: suspected iNPH patients with no objective symptoms. Lateral ventricle dilation (Evans index>0.3), narrowed subarachnoid spaces at the high convexity, and dilation of sylvian fissure and basal cistern are observed in the patient.

Table 1
Demographic data.

Subjects	Age	Sex	Chief complaint	Educational attainment	Mobidity duration
AOS1	75	F	Amnesia	10	2
AOS2	74	M	Gait disturbance	16	3
AOS3	68	F	Gait disturbance	9	1
AOS4	79	F	Gait disturbance	16	2
AOS5	71	M	Gait disturbance	16	4
AOS6	72	M	Gait disturbance	9	3
AOS7	76	M	Gait disturbance	14	5
NOS1	80	M	Amnestic complaint	13	5
NOS2	71	F	Amnestic complaint	14	6
NOS3	72	M	Amnestic complaint	9	3
NOS4	80	M	Feeling unstable walking	13	6
NOS5	72	M	Feeling unstable walking	16	1
NOS6	70	M	Feeling unstable walking	16	1
NOS7	64	M	Feeling unstable walking	16	0.5
NC1	73	M	NA	12	NA
NC2	79	M	NA	16	NA
NC3	70	M	NA	12	NA
NC4	79	M	NA	16	NA
NC5	68	F	NA	12	NA
NC6	71	F	NA	12	NA
NC7	78	F	NA	15	NA

M : male, F : female.
AOS : iNPH patients with apparent objective triad symptoms , NOS: suspected iNPH patients with no objective triad symptoms, NC : normal controls. The seven patients with AOS were numbered AOS1 to AOS7, the seven patients with NOS were numbered NOS1 to NOS7, and the seven normal controls were numbered NC1 to NC7.

control subjects in this study were having (1) the Mini-mental State Examination (MMSE) [26] scores of over 27, (2) ability to walk 1 km without assistance, (3) availability of reliable informants, (4) full scores on the Physical Self-Maintenance Scale (PSMS) and the Instrumental Activity of Daily Living Scale (IADL) [27] rated by their informants, (5) normal MR images, without ventriculomegaly or narrowed subarachnoid spaces at the high convexity, (6) normal Magnetic Resonance Angiography, and (7) willingness to undergo SPECT scan with the method as described in SPECT procedure. The exclusion criteria in this study were (1) existence of neurological or psychiatric disease in the past or in their current medical history, (2) head injury with unconsciousness for more than 1 h, and (3) undergoing active therapy for life-threatening cancers or poor condition due to a chronic disease. In the 34 normal elderly control subjects, 11 (seven males and four females) had undergone the same types of cognitive and gait tests that the NOS and AOS subjects had undergone. We selected four males and three females from these 11 subjects in the database that matched the NOS subjects in age (within 5 years). The normal controls (NC) had a mean age of 74.0 ± 4.6 years (range, 68–79 years) and a mean educational attainment of 13.6 ± 2.0 years (range, 12–16 years).

There was no significant difference among the three groups, with respect to age ($F(2,18) = 0.14$, $p = 0.87$, one-way ANOVA), sex ($p = 0.60$, Fisher's exact test) or educational attainment ($F(2,18) = 0.25$, $p = 0.78$, one-way ANOVA). There was also no significant difference between NOS and AOS in morbidity duration ($F(1,12) = 0.11$, $p = 0.74$, one-way ANOVA).

2.2. Evaluation of cognitive and gait functions

Cognitive examinations were administered to the iNPH patients, including MMSE [26], Frontal Assessment Battery (FAB) [28], selective attention test of Trail Making Test (TMT A) [29], Attention/Concentration (AC) subtest of the Wechsler Memory Scale-Revised (WMS-R) [30], and subtest of the picture recognition and subtest of the immediate and delayed recall of a short story of the Rivermead Behavioural Memory Test (RBMT) [31]. The MMSE is one of the most widely used screening instruments for dementia and provides a total score ranging from 0 to 30, with lower scores indicative of greater cognitive impairment [26]. The FAB is a simple tool for assessing frontal lobe symptoms [28]. TMT A is a neuropsychological test for evaluating psychomotor speed [29].

Gait disturbance was evaluated with the Timed Up & Go Test (TUG) [32], which has been used to evaluate walking ability [33,34] and gait disturbance in iNPH patients [22]. This test measures the total time it takes a subject to perform a series of movements, or, sitting in an armchair to stand up, walk forward 3 meters, and return to the seated position.

As for NC subjects, we gained the data of evaluations of cognitive and gait functions from the database for the previous study [25].

2.3. MR imaging procedure

MR imaging for patients with AOS and NOS, was performed on a 1.5-T system (Signa Excite HD 12.x, General Electric Medical Systems, Milwaukee). A three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections that cover the whole calvarium. The operating parameters were as follows: field of view = 240 mm, matrix = 256×256, 124×1.40 mm contiguous sections, TR = 12.55 ms, TE = 4.20 ms, and flip angle = 15°.

2.4. SPECT procedure

Regional CBF was quantitated by N-isopropyl-p-[123I] iodoamphetamine (123I-IMP) autoradiography (ARG) using a SPECT scanner (SPECT-2000H, Hitachi Medical Co., Tokyo, Japan). The scanner has a four-head rotating camera. The scanner, fitted with low-energy, medium-resolution collimators, has as intrinsic spatial resolution of 13-mm full width at half maximum (FWHM) in-plane and axially. Scanning was initiated 15 min after 1-min intravenous infusions of 167 MBq of [123I]IMP and physiological saline into a brachial artery, each delivered at a constant rate of 1.5 ml/min. Scan duration was 26.7 min (mid-scan time = 28.3 min). Two milliliters of arterial blood was taken from the opposite brachial artery at 10–14 min post-IMP administration. The radioactivity concentration of the blood was measured with a well counter cross-calibrated with SPECT. The partial pressures of O2 and CO2, and pH of the blood were measured with a blood gas tension analyzer. The projections of the SPECT scan were acquired by a 360° continuous rotation of the camera. The images were reconstructed using filtered back-projection with a Butterworth filter (Cut-off = 0.20, Nyquist; order = 10), in which attenuation was corrected numerically with an attenuation coefficient of 0.08 cm^{-1} [35].

Quantitative rCBF values were calculated based on the 2-compartment model analysis of IMP, with the assumption that the distribution volume (Vd) was 40.0 ml/ml. Regional CBF maps were calculated pixel by pixel (64×64 matrix size) from the SPECT data and the standard input function was calibrated by one-point arterial blood sampling.

2.5. Regions of interest (ROIs) analysis

We used the ROI method to evaluate rCBF in each subject and compared the rCBF among AOS, NOS, and NC subjects. Thirty-five ROIs were used in this study. Fig. 2 shows the location of the ROIs on brain template images. A monitor screen displayed each patient's MR image together with the corresponding brain slice templates. One investigator (M.T.), who specializes in neuroimaging, and who was blind to the subject's clinical information, manually placed the ROIs, each a circle 11 mm diameter on MR images of each subject, while referring to the brain template images. Then, he coregistered each MR image and the corresponding SPECT image using Neurological Statistical Image Analysis Software (NEUROSTAT) [36], and quantified the rCBF

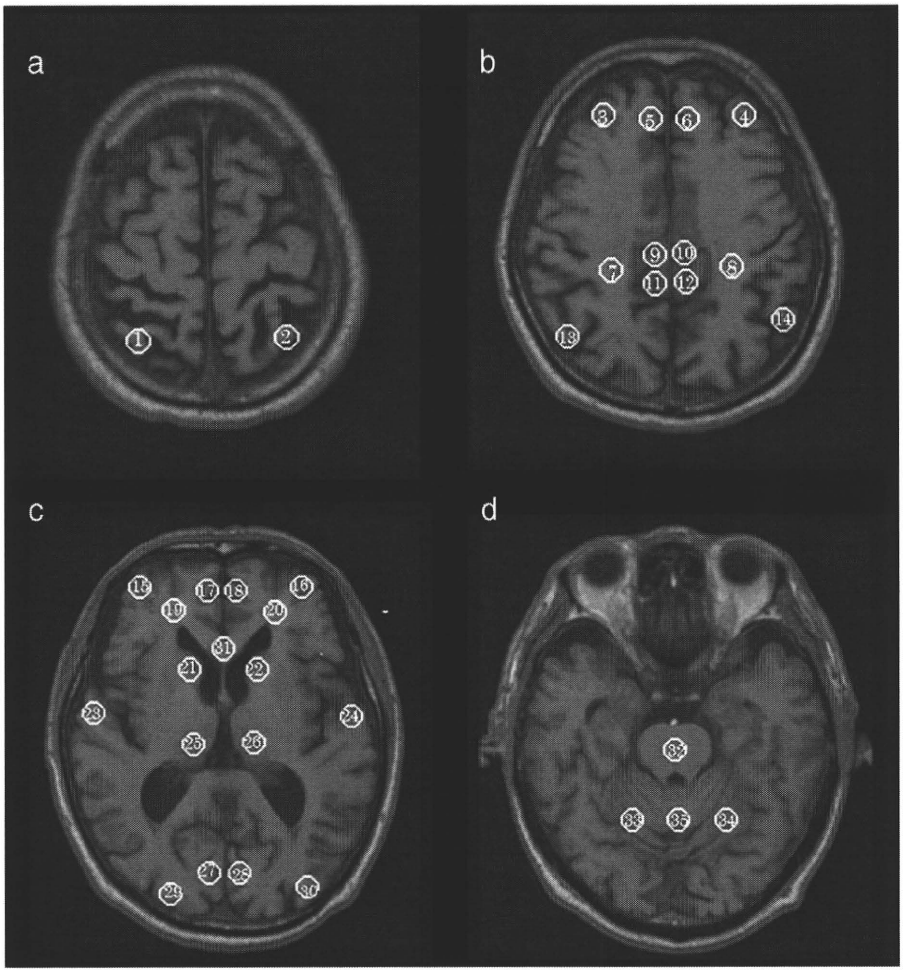

Fig. 2. Brain templates displaying ROIs on axial MR images of a normal brain Thirty-five regions of interest (ROIs), numbered from 1 to 35, are located in these four slices of MR images parallel to the AC-PC line. The 35 ROIs were lumped into 16 regions (Table 3) and quantitative rCBF was averaged for each region. (a) superior parietal lobe level ; (b) posterior cingulate gyrus and precuneus level ; (c) thalamus level ; (d) pons level.

of the 35 ROIs of each subject. ROI location and quantitative rCBF measurement were performed twice (test and retest) in order to determine the test–retest reliability, although only the data obtained in the first test were used in the comparisons of the three groups. We classified the 35 ROIs into 16 regions (listed in Table 3).

2.6. Statistical analysis

Demographic, clinical and rCBF data were analyzed with JMP8 (SAS Institute Inc, Cary, NC, USA). The NOS, AOS and NC groups were compared with one-way analysis of variance (ANOVA). A post-hoc Turkey-Kramer HSD test was used when appropriate. The level of statistical significance was set at $p<0.05$. Test–retest reliability was assessed by the intraclass correlation coefficient (ICC) [37].

3. Results

3.1. Cognitive and gait assessment

One-way ANOVA revealed significant differences among the three groups in all the cognitive tests (Table 2). Post-hoc tests showed that the scores of AOS were significantly worse than those of NC in all the cognitive tests. Although the mean scores of the NOS group were between those of the NC and AOS groups in all the cognitive tests, there were no significant differences between NOS and NC. The differences between NOC and AOS were significant in MMSE, FAB, the Attention/Concentration subtest of the WMS-R, and the immediate recall of a short story subtest of the RBMT, but not in TMT-A, or the subtests of picture recognition and delayed recall of a short story of the RBMT.

As for gait evaluation, the TUG scores of the NC and NOS groups were significantly lower (i.e. better) than those of the AOS group.

3.2. Comparison of quantitative rCBF

The ICCs, which assessed the test–retest reliability, was 0.96 for all 35 ROIs and ranged from 0.79 to 0.99 in 16 brain regions (Table 3), indicating high reliability of the ROI method used in this study.

One-way ANOVA showed significant differences in the quantitative rCBF in all regions among the three groups (Table 3). Post-hoc Tukey–Kramer HSD tests revealed that the quantitative rCBF of the NOS group was significantly less than that of the NC group in all regions except for in the frontal white matter, and that the quantitative rCBF of the AOS group was significantly less than that of the NC group in all regions (Table 3). Additionally no significant differences of quantitative rCBF were observed between the NOS and AOS groups in any of the regions (Table 3).

4. Discussion

In this study, we evaluated the quantitative rCBF of suspected iNPH patients who had specific MR image features of iNPH (enlarged sylvian fissures together with ventriculomegaly and narrowed subarachnoid spaces at the high convexity), but who did not have

Table 2
Results of cognitive and gait evaluations.

Cognitive and gait tests	Scores of tests			Statistical analysis		
	Average ± SD			One-way ANOVA	Tukey–Kramer HSD	
	AOS	NOS	NC	F value, p value		
MMSE (possible range 0–30)	21.1 ± 6.8	27.9 ± 1.3	29.1 ± 1.1	F(2,18) = 7.84, P = 0.0036	AOS<NOS[a]	AOS<NC[b]
FAB (possible range 0–18)	10.8 ± 2.6	14.4 ± 1.4	15.9 ± 1.3	F(2,17) = 13.06, P = 0.0004	AOS<NOS[b]	AOS<NC[c]
TMT A (seconds)	108.3 ± 67.4	53.1 ± 17.1	39.6 ± 17.0	F(2,17) = 5.44, P = 0.0149		AOS>NC[a]
WMS-R AC index	81.7 ± 17.7	101.9 ± 10.1	107.1 ± 11.7	F(2,17) = 6.47, P = 0.0081	AOS<NOS[a]	AOS<NC[b]
RBMT picture recognition (possible range 0–10)	8.2 ± 1.7	9.1 ± 0.9	10.0 ± 0	F(2,17) = 4.69, P = 0.0239		AOS<NC[a]
RBMT immediate story recall (possible range 0–25)	5.5 ± 3.1	11.1 ± 3.5	11.7 ± 2.3	F(2,17) = 8.20, P = 0.0032	AOS<NOS[b]	AOS<NC[b]
RMBTdelayed story recall (possible range 0–25)	4.1 ± 3.4	7.9 ± 4.6	9.8 ± 3.3	F(2,17) = 3.62, P = 0.0489		AOS<NC[a]
TUG (seconds)	14.3 ± 3.4	10.5 ± 1.5	10.5 ± 1.7	F(2,17) = 6.05, P = 0.0104	AOS>NOS[a]	AOS>NC[a]

AOS : iNPH patients with apparent objective triad symptoms, NOS: suspected iNPH patients with no objective triad symptoms, NC : normal controls.
MMSE: Mini-Mental State Examination (possible range 0–30), FAB: Frontal Assessment Battery (possible range 0–18), TMT A: Trail Making Test A (seconds), WMS-R AC: Wechsler Memory Scale Revised attention/concentration (index), RBMT picture: subtest of the picture recognition of the Rivermead Behavioural Memory Test (possible range 0–10), RBMT immediate story recall : subtest of the immediate story recall of the Rivermead Behavioural Memory Test (possible range 0–25), RBMT delayed story recall : subtest of the delayed story recall of the Rivermead Behavioural Memory Test (possible range 0–25), TUG : Timed Up & Go Test (seconds).
[a] p value<0.05.
[b] p value<0.01.
[c] p value<0.001.

Table 3
Intraclass correlation coefficients (ICCs) and quantitative rCBF of each brain region.

Brain region	ROI Number	ICC	Quantitative rCBF			One-way ANOVA		Tukey-Kramer HSD		
			Average (ml/100 g/min) ± SD					p value		
			AOS	NOS	NC	F (2,18)	p value	Between AOS and NC	Between NOS and NC	Between AOS and NOS
SPL	1, 2	0.85	18.0 ± 8.0	20.4 ± 3.9	37.0 ± 3.7	24.17	p<0.0001	AOS<NC p<0.0001	NOS<NC p<0.0001	p = 0.6924
IPL	13, 14	0.94	20.5 ± 8.1	22.5 ± 4.9	42.1 ± 4.0	28.43	p<0.0001	AOS<NC p<0.0001	NOS<NC p<0.0001	p = 0.7953
LFC	3, 4, 15, 16	0.99	22.8 ± 7.0	27.8 ± 5.2	47.7 ± 5.8	33.40	p<0.0001	AOS<NC p<0.0001	NOS<NC p<0.0001	p = 0.2915
LTC	23, 24	0.97	23.9 ± 2.9	21.4 ± 3.6	48.4 ± 5.5	90.13	p<0.0001	AOS<NC p<0.0001	NOS<NC p<0.0001	p = 0.5168
LOC	29, 30	0.99	28.4 ± 5.7	24.5 ± 4.8	43.1 ± 6.4	21.03	p<0.0001	AOS<NC p = 0.0003	NOS<NC p<0.0001	p = 0.4287
MFC	5, 6, 17, 18	0.99	27.3 ± 6.8	30.6 ± 7.5	49.2 ± 7.0	19.22	p<0.0001	AOS<NC p<0.0001	NOS<NC p = 0.0003	p = 0.6677
MOC	27, 28	0.97	35.2 ± 10.4	34.2 ± 5.1	54.6 ± 6.7	15.51	p = 0.0001	AOS<NC p = 0.0005	NOS<NC p = 0.0003	p = 0.9685
PCP	9, 10, 11, 12	0.89	30.4 ± 5.3	26.4 ± 7.5	47.4 ± 10.5	13.50	p = 0.0003	AOS<NC p = 0.0025	NOS<NC p = 0.0003	p = 0.6219
FWM	19, 20	0.98	19.5 ± 5.3	23.2 ± 5.8	30.7 ± 5.5	7.32	p = 0.0047	AOS<NC p = 0.0040	p = 0.0530	p = 0.4515
SC	7, 8	0.79	21.8 ± 5.2	18.9 ± 8.1	31.7 ± 5.1	8.02	p = 0.0032	AOS<NC p = 0.0216	NOS<NC p = 0.0034	p = 0.6753
GCC	31	0.92	12.4 ± 3.2	11.9 ± 5.7	22.5 ± 3.0	14.28	p = 0.0002	AOS<NC p = 0.0008	NOS<NC p = 0.0005	p = 0.9691
HCN	21, 22	0.97	21.9 ± 6.1	23.7 ± 4.4	43.8 ± 6.4	31.69	p<0.0001	AOS<NC p<0.0001	NOS<NC p<0.0001	p = 0.8240
TH	25, 26	0.99	25.1 ± 6.1	28.3 ± 5.2	54.6 ± 9.0	38.17	p<0.0001	AOS<NC p<0.0001	NOS<NC p<0.0001	p = 0.6611
PN	32	0.99	23.6 ± 9.1	28.1 ± 4.0	46.0 ± 5.8	22.34	p<0.0001	AOS<NC p<0.0001	NOS<NC p = 0.0002	p = 0.4203
HCB	33, 34	0.98	31.7 ± 11.6	33.9 ± 7.5	55.7 ± 9.3	13.25	p = 0.0003	AOS<NC p = 0.0006	NOS<NC p = 0.0014	p = 0.9083
VCB	35	0.96	33.5 ± 11.0	32.5 ± 5.3	56.1 ± 10.4	14.54	p = 0.0002	AOS<NC p = 0.0007	NOS<NC p = 0.0004	p = 0.9774

SPL, superior parietal lobe ; IPL, inferior parietal lobe ; LFC, lateral frontal cortex ; LTC, lateral temporal cortex ; LOC, lateral occipital cortex ; MFC, medial frontal cortex ; MOC, medial occipital cortex ; PCP, posterior cingulate gyrus and precuneus ; FWM ; frontal white matter ; SC, semioval center ; GCC, genu of corpus callosum ; HCN, head of caudate nucleus ; TH, thalamus ; PN, pons ; HCB, hemisphere of cerebellum ; VCB, vermis of cerebellum.
AOS : iNPH patients with apparent objective symptoms, NOS: suspected iNPH patients with no objective symptoms, NC : normal controls.
rCBF : regional cerebral blood flow.

any apparent objective triad symptoms. The NOS group did not significantly differ from the NC group in any of the cognitive or gait evaluations, although the lack of significant difference might be due to a type II error because of the small sample size of this study. In all brain regions examined except for in the frontal white matter, the quantitative rCBF of the NOS group was significantly less than that of the NC group. Although the difference of the quantitative rCBF in the frontal white matter between the NOS and NC groups did not reach the significant level, the trend (p value = 0.0530) that the quantitative rCBF of the NOS group was less than that of the NC group was shown in this region. The NOS group did not significantly differ from the AOS group in the quantitative rCBF in any of the regions, although the lack of significant difference might be due to a type II error because of the small sample size.

Two methods are generally used to compare rCBF values among different groups, the ROI method and voxel-based statistical image-analyzing methods. Advantages of the latter are that they can analyze rCBF automatically and absolutely in a user-independent fashion and can analyze rCBF of the whole brain easily, making it better than the ROI method for many subjects. A disadvantage of the voxel-based methods is that they work poorly with patients with severely distorted brains, which are difficult to normalize in SPM [7,17] or in 3D-SSP [18], leading to incorrect results. On the other hand, the ROI method can avoid the distortion problem by using MR image templates to locate the ROIs on anatomically precise regions. The main disadvantage of the ROI method is that it has an inherent arbitrariness based on how the regions are selected. For patients with iNPH-specific severely distorted brains, the ROI method is more suitable than the voxel-based statistical image-analyzing methods and was used to compare the rCBF values among the AOS, NOS, and NC subjects in this study. The ICCs for measuring the rCBF in different regions (0.79 to 0.99) were higher than those in other ROI analyses [38,39], and indicate high reliability of the ROI method used in this study. However, we could not completely erase the arbitrariness that necessarily accompanies the ROI method. Another problem was that an investigator, even though blinded to the subjects' clinical information, could distinguish MR images of the NC subjects from those of the AOS and NOS subjects. However, because the MR images of AOS and NOS were indistinguishable, the investigator was completely blind to whether iNPH-like MR images were those of AOS or NOS.

The NOS patients were probably in the very early stage of iNPH because their MR images showed enlarged sylvian fissures together with ventriculomegaly and narrowed subarachnoid spaces at the high convexity, which are not observed in patients with disease other than iNPH. "High (superior) convexity" was first used by Kitagaki, et al [4] to indicate the suprasylvian subarachnoid space. Although many researchers have used "high convexity" [2], the term has not been defined strictly. However, "high convexity" covers the superior parietal lobe. In addition, the mean scores of all the cognitive tests in the NOS group were located between those of the NC and AOS groups, although there were no significant differences between the NOS and NC groups in any of the cognitive tests. The NOS group showed no gait disturbance at all. The slight cognitive impairment with no gait disturbance in patients with NOS in this study was consistent with findings of the first report of AVIM [2]. In that study, two of the eight subjects who were diagnosed as AVIM at their first examination subsequently showed cognitive deterioration and were diagnosed as having iNPH.

Our finding that rCBF of the NOS group was reduced just as much as in the AOS group was not what we hypothesized. The fact that rCBF was equally reduced in the AOS and NOS groups suggests that factors other than reduced rCBF are involved in the manifestation of symptoms in iNPH patients. Possible factors include (1) low availability of striatal D2 receptor, which is associated with hypokinetic gait and anhednic mentation in iNPH patients [40], (2) the compressive effect of the ventricles on several brain areas [41–43], (3) apoptosis of neuronal cells [44], and (4) dysfunction of the neurons [45].

A limitation of our study is the small sample size. Another limitation is that our study was based only on cross sectional data, and not on longitudinal data. We intend to monitor the NOS group in this study to see if they develop objective iNPH symptoms. Third, we did not attempt to closely match the degrees of ventriculomegaly and narrowing of the sulci at the high convexity between the NOS and AOS patients. The degree of morphological change in the brain might be different between the two groups. These issues should be taken into consideration before the findings can be generalized.

In this study, we were unable to identify the neuroanatomical bases of the triad symptoms by quantitative rCBF analyses of NOS and AOS patients. Our results indicate that hypoperfusion developed in all brain regions before the appearance of the triad symptoms and was not correlated with the degree of symptoms in patients with iNPH. Further studies that compare factors other than rCBF between iNPH patients with NOS and AOS should provide some clues to the pathogenesis of iNPH.

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